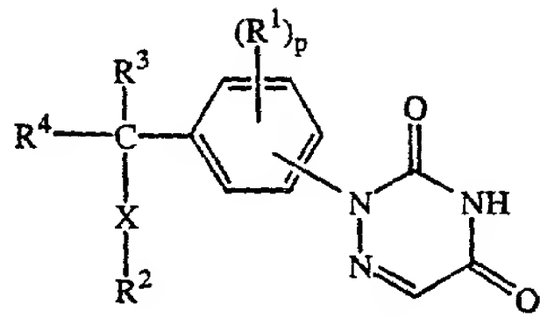
Claims

1. A compound having the formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR^5 or a direct bond;

Y represents O, S, NR^5, or $S(O)_2$;

each R^1 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

R^2 represents Het^1, C_{3-7}cycloalkyl, C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^5, then R^2 may also represent aminocarbonyl, aminothiocarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl;

R^3 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl; or

R^3 and R^4 taken together form a C_{2-6}alkanediyl;

R^5 represents hydrogen or C_{1-4}alkyl;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl or mono-or di(C_{1-4}alkyl)aminoC_{1-4}alkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, arylcarbonyl, Het^3carbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3, Het^4 and R^6;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, phenylcarbonyl, Het^3carbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3, Het^4 and R^6;

each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, C(=O)NR^7R^8, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, phthalimide-2-yl, Het^3 and C(=O)Het^3;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylamino-carbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14} and R^6;

each R^{14} independently represents hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, aminocarbonylmethylene or mono-or di(C_{1-4}alkyl)aminocarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cyclo-alkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, C(=O)NR^9R^{10}, C(=O)-O-R^{14}, R^6, -O-R^6, phenyl, Het^3, C(=O)Het^3 and C_{1-4}alkyl substituted with hydroxy, C_{1-4}alkyloxy, C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 or NR^9R^{10};

Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each

independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^2 and R^{11};

Het^2 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^4, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^4 and R^{11};

Het^3 represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, C(=O)-O-R^{14}, R^6 and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, R^6 and $NR^{12}R^{13}$;

Het^4 represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl.

2. A compound as claimed in claim 1 wherein each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, aryl-carbonyl, Het^3carbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkyl-carbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 and R^6;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, phenylcarbonyl, Het^3carbonyl,

C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 and R^6;

R^{11} is being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, $C(=O)NR^7R^8$, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, phthalimide-2-yl, Het^3, Het^4 and $C(=O)Het^3$; and

Het^2 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]-pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo-[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from R^{11}.

3. A compound as claimed in claim 1 or 2 wherein the compound of formula (I) contains an ester function.

4. A compound as claimed in any one of claims 1 to 3 provided that those compounds wherein X is a direct bond, at least one of R^3 and R^4 is hydrogen, and R^2 is 3-pyridinyl optionally substituted in the 6 position with an optionally substituted alkyl or acyl group are excluded.

5. A compound as claimed in any one of claims 1 to 4 wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

6. A compound as claimed in any one of claims 1 to 5 wherein R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl,

oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}.

7. A compound as claimed in any one of claims 1 to 6 wherein R^3 and R^4 are both methyl and -X-R^2 is Het^1.

8. A compound as claimed in any one of claims 1 to 7 wherein p is 1 or 2 and each R^1 is chloro.

9. A compound as claimed in any one of claims 1 to 8 wherein R^3 and R^4 are both methyl, -X-R^2 is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

10. A compound as claimed in claim 1 wherein the compound is
2-[3,5-dichloro-4-[1-methyl-1-(4-phenyl-2-thiazolyl)ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-[4-(3-chlorophenyl)-5-methyl-2-thiazolyl]-1-methylethyl]-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-(5-phenyl-1,2,4-oxadiazol-3-yl)ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-(4,5-diphenyl-2-thiazolyl)-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]ethyl]-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-(4-methyl-5-phenyl-2-thiazolyl)ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[4-phenyl-5-(3-pyridinyl)-2-thiazolyl]ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[4-phenyl-5-(phenylmethyl)-2-thiazolyl]ethyl]-phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[5-(4-pyridinyl)-1,2,4-oxadiazol-3-yl]ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;

2-[3,5-dichloro-4-[1-methyl-1-[4-(3-thienyl)-2-thiazolyl]ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-[4-(2-furanyl)-2-thiazolyl]-1-methylethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[5-(3-pyridinyl)-1,2,4-oxadiazol-3-yl]ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-[5-(2-methyl-3-pyridinyl)-1,2, 4-oxadiazol-3-yl]ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione;
2-[3,5-dichloro-4-[1-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione; a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

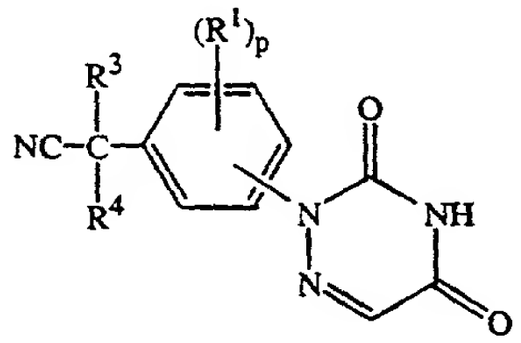
11. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 10.

12. A process for preparing a composition as claimed in claim 11, , wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 10.

13. A compound as claimed in any one of claims 1 to 10 for use as a medicine.

14. Use of a compound as claimed in any one of claims 1 to 10 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.

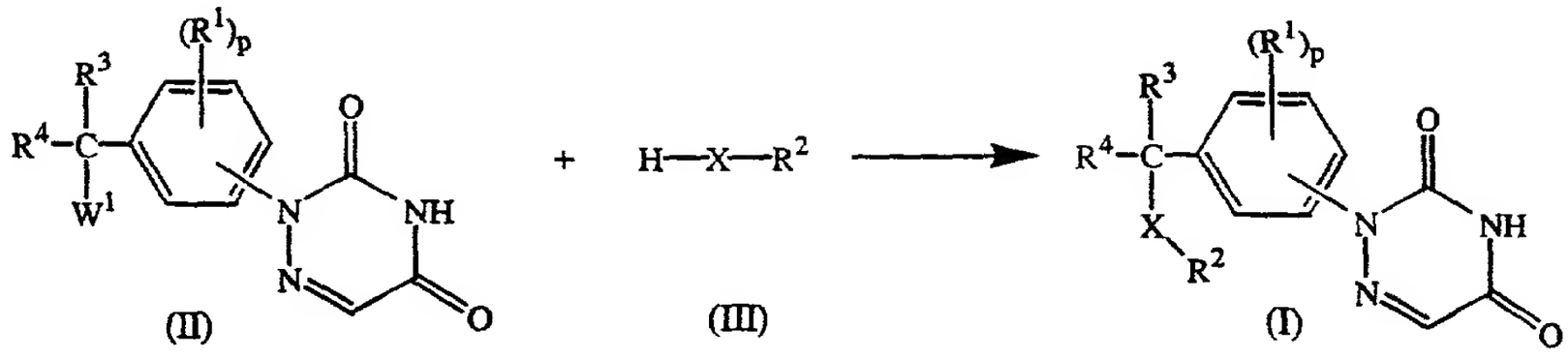
15. A compound of formula



(XI-a)

wherein R^1, R^3, R^4 and p are as defined in claim 1.

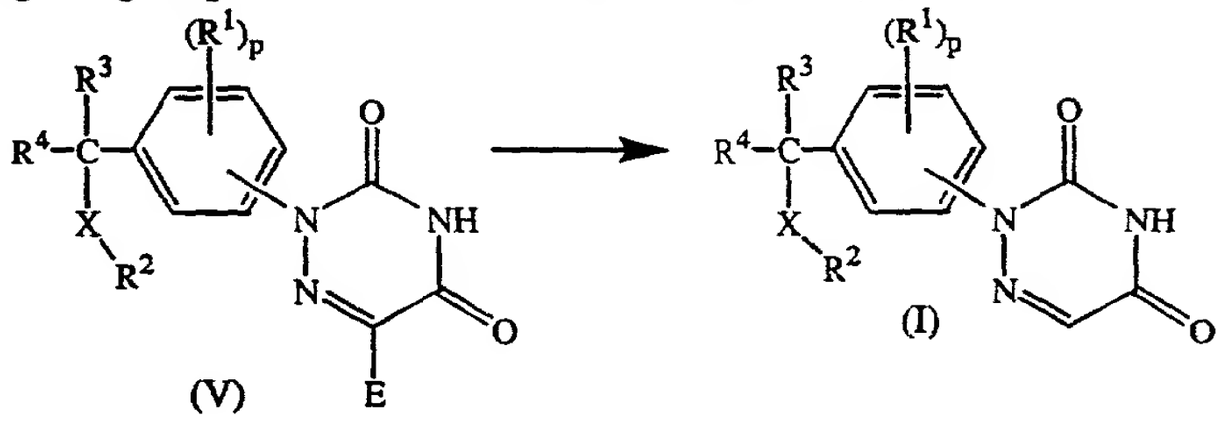
16. A process for preparing a compound as claimed in claim 1, characterized by,
a) reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group with an appropriate reagent of formula (III) optionally in a reaction-inert solvent and optionally in the presence of a base at a temperature ranging between - 70°C and reflux temperature;



(II) (III) (I)

wherein R^2, R^3, R^4, p and X are as defined in claim 1;

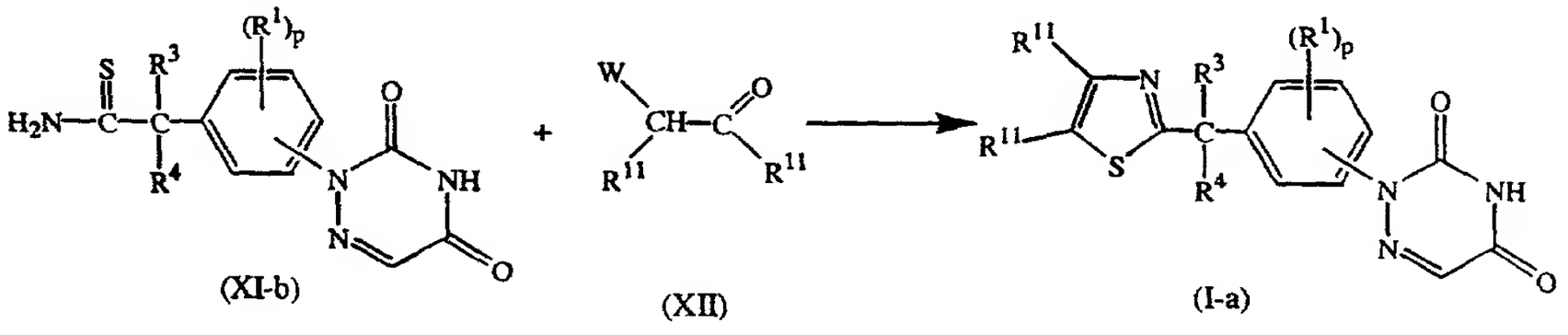
b) eliminating the group E of a triazinedione of formula (V)



(V) (I)

wherein E is an appropriate electron attracting group and R^1, R^2, R^4, X and p are as defined in claim 1;

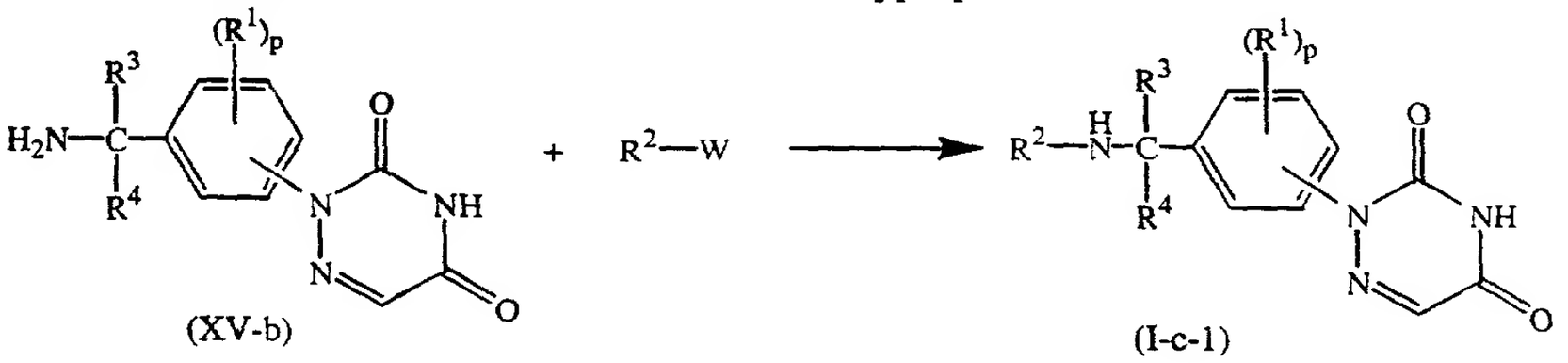
c) cyclizing a thioamide of formula (XI-b) with an intermediate of formula (XII) in a suitable solvent



(XI-b) (XII) (I-a)

wherein W is a suitable leaving group, and R^1, R^3, R^4 and p are as defined in claim 1; thus forming a compound of formula (I-a);

d) reacting an amine derivative of formula (XV-b) with an intermediate of formula R^2-W or with a functional derivative thereof in an appropriate solvent



(XV-b) (I-c-1)

wherein W is a suitable leaving group and R^1, R^2, R^3, R^4 and p are as defined in claim 1;

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

17. A process of marking a receptor comprising the steps of
    a) radiolabelling a compound as defined in claim 1;
    b) administering said radiolabelled compound to biological material,
    c) detecting the emissions from the radiolabelled compound.

18. A process of imaging an organ, characterized by, administering a sufficient amount of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.